REMARKS

The Present Invention

The invention is drawn to a method of enhancing bone density or formation, an adenoviral vector, and a bone graft.

The Pending Claims

Upon entry of this amendment, claims 1-3, 9, 11, 12, 17, 19, 21, 22, 25, 30, 32, 33, 40, 42-47, 48-50, 52-56, 58, and 59-71 will be pending. Claims 1-3, 11, 12, 17, 44-50, 63, 66, and 67 are directed to the method, claims 19, 21, 42, 43, 52-56, 64, 68, and 69 are directed to the adenoviral vector, and claims 22, 25, 32, 33, 58, 59-62, 65, 70, and 71 are directed to the bone graft.

Discussion of Claim Amendments

Claim 1 has been amended to incorporate the subject matter of claims 4, 6, and 9, and a portion of claim 7, and to delete reference to VEGFs other than VEGF 121. Claim 19 has been amended to incorporate the subject matter of claim 26 and a portion of the subject matter of claim 38, as well as to delete reference to VEGFs other than VEGF 121. Claim 22 has been amended to incorporate the subject matter of claim 27 and a portion of the subject matter of claim 23, and to delete reference to VEGFs other than VEGF 121. Claims 44, 52, and 58 have been amended to delete reference to osteogenic proteins other than HBNF and midkine, and to add reference to TGF-β1. This amendment is supported by the specification at, for example, page 3, lines 26-28. Claims 4, 6-8, 10, 18, 23, 26, 27, 29, 31, 38, 39, 41, 51, and 57 have been cancelled. Claims 9, 11, 12, and 17 have been amended to change claim dependency in view of the cancellation of claim 6. Claims 63-71 are new and are merely dependent claims that separately recite one or more elements recited in the corresponding independent claims. Accordingly, no new matter has been added by way of these amendments.

The Office Action

The Office Action raises the following concerns:

(a) claims 1-3, 6, 17-19, 21, 22, 25, 44, 45, 48-53, 56-59, and 62 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over each of the disclosures of WO 95/24473 (Hu et al.) and U.S. Patent 5,935,820 (Hu et al.),

(b) claims 1, 3, 6-8, 17, 18, 22, 23, 25, 29, 44, 45, 48-53, 56-59, and 62 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over the combined disclosures of U.S. Patent 6,398,816 (Breitbart et al.) and U.S. Patent 5,935,820 (Hu et al.),

(c) claims 1, 2, 6-8, 10, 17, 18, 44, 45, 48-53, 56-59, and 62 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over the combined disclosures of U.S. Patent 6,525,030 (Eriksson) and U.S. Patent 6,475,480 (Mehtali et al.), and

(d) claims 4, 9, 11, 12, 26, 27, 30, 32, 33, 38-43, 46, 47, 54, 55, 60, and 61 are objected to as being dependent on a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claims and any intervening claims.

Reconsideration of the Section 103 rejections is hereby requested.

Discussion of Rejections Under 35 U.S.C. § 103

Claims 1-3, 6, 17-19, 21, 22, 25, 44, 45, 48-53, 56-59, and 62 have been rejected under Section 103 as allegedly being obvious over each of the disclosures of WO 95/24473 ("the 473 PCT application") and U.S. Patent 5,935,820 ("the '820 patent"). These rejections are respectfully traversed for the reasons set forth below.

To establish a *prima facie* case of obviousness under Section 103 based on a combination of references, (i) the references must disclose or suggest every element of the claimed invention, (ii) there must be a motivation to combine the references, and (iii) the combination of references must provide a reasonable expectation of success for making the claimed invention. M.P.E.P. § 2143.

The Office Action contends that both the '473 PCT application and the '820 patent disclose the use of a polynucleotide encoding VEGF2 to promote bone growth, which can be delivered via adenoviral delivery to cells either *ex vivo* or *in vivo*. The '473 PCT application and the '820 patent also allegedly disclose different VEGF isoforms (e.g., 121, 165, 189, and 206) that promote angiogenesis and wound healing. The Office Action contends that, because the different VEGF isoforms were known to have the same function, one of ordinary skill in the art would have been motivated to use VEGFs other than VEGF2 to promote bone growth, and would have anticipated a reasonable expectation of success in doing so. The Office Action further alleges that the claims should be construed to include the use of any VEGF as the osteogenic protein, since claims 18, 51, and 57 recite that the first and second nucleic acids can be the same.

Applicants note that Claims 18, 51, and 57 have been cancelled. Neither the '473 PCT application nor the '820 patent discloses or suggests using VEGF 121 alone or in

combination with the specific osteogenic proteins recited in claims 1, 19, and 22, or a VEGF in combination with HBNF, TGF-β1, or midkine, as recited in claims 44, 52, and 58, to enhance bone density or formation. Thus, neither the '473 PCT application nor the '820 patent discloses or suggests the subject matter of the pending claims.

Claims 1, 3, 6-8, 17, 18, 22, 23, 25, 29, 44, 45, 48-53, 56-59, and 62 have been rejected under Section 103 as allegedly being obvious over the combined disclosures of U.S. Patent 6,398,816 ("the '816 patent") and the '820 patent. This rejection is respectfully traversed for the reasons set forth below.

The '816 patent allegedly discloses using an adenoviral vector encoding one or more bioactive molecules (e.g., VEGF, BMPs, and PDGF) to transduce cells (e.g., periosteal cells), whereby the genetically engineered cells can be incorporated into a prosthesis for tissue (e.g., bone or cartilage) repair. The '816 patent does not cure the deficiencies of the '820 patent discussed above. Namely, the '816 patent does not disclose or suggest the use of adenoviral vectors or bone grafts comprising VEGF 121 in combination with one of the specific osteogenic proteins recited in claims 1 and 22, or comprising a VEGF in combination with HBNF, TGF-β1, or midkine, as recited in claims 44, 52, and 58, to enhance bone growth or formation. As such, the combination of the '816 patent and the '820 patent does not disclose or suggest the subject matter of the pending claims.

Claims 1, 2, 6-8, 10, 17, 18, 44, 45, 48-53, 56-59, and 62 have been rejected under Section 103 as allegedly being obvious over the combined disclosures of U.S. Patent 6,525,030 ("the '030 patent") and U.S. Patent 6,475,480 ("the '480 patent"). This rejection is respectfully traversed for the reasons set forth below.

The '030 patent allegedly discloses a method for stimulating bone growth by delivering an aqueous solution of gene that promotes bone growth (e.g., VEGF, FGF, and TGF-beta) to periosteal cells *in vivo* by microneedle injection. The '030 patent does not disclose the use of an adenoviral vector for gene delivery. The disclosure of the '480 patent allegedly cures the deficiencies in the '030 patent by allegedly disclosing an adenoviral vector encoding a gene of interest, which provides for improved gene expression in a mammal. The Office Action concludes that one of ordinary skill in the art would have been motivated to modify the disclosure of the '030 patent and employ an adenoviral vector as disclosed in the '480 patent to increase expression of the bone-growth promoting gene.

Neither the '030 patent nor the '480 patent discloses or suggests the use of adenoviral vectors or bone grafts comprising VEGF 121 in combination with one of the specific osteogenic proteins recited in claim 1, or comprising a VEGF in combination with HBNF, TGF-β1, or midkine, as recited in claims 44, 52, and 58, to enhance bone growth or

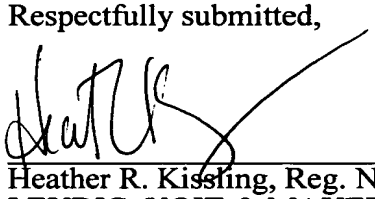
formation. As such, the combination of the '030 patent and the '480 patent does not disclose or suggest the subject matter of the pending claims.

Accordingly, because the all of the elements of the pending claims are not disclosed or suggested by any of the cited prior art references, the pending claims define novel and unobvious subject matter in view of the '473 PCT application, the '820 patent, the '816 patent, the '030 patent, and the '480 patent, either alone or in combination. Thus, the Section 103 rejections based on these references should be withdrawn.

Conclusion

The application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned agent.

Respectfully submitted,



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